

NDA 11-790/S-046

Page 3

Additions are underlined and deletions are ~~strickethrough~~

ROBAXIN[®] Injectable

(methocarbamol injection, USP)

Rx Only

DESCRIPTION

ROBAXIN[®] (methocarbamol injection, USP) Injectable, a carbamate derivative of guaifenesin, is a central nervous system (CNS) depressant with sedative and musculoskeletal relaxant properties. It is a sterile, pyrogen-free solution intended for intramuscular or intravenous administration. Each mL contains: methocarbamol, USP 100 mg, polyethylene glycol 300, NF 0.5 mL, Water for Injection, USP q. s. The pH is adjusted, when necessary, with hydrochloric acid and/or sodium hydroxide. The chemical name of methocarbamol is 3-(2-methoxyphenoxy)-1,2-propanediol 1-carbamate and has the empirical formula of C₁₁H₁₅NO₅. Its molecular weight is 241.24. The structural formula is shown below:

[insert structural formula]

Methocarbamol is a white powder, sparingly soluble in water and chloroform, soluble in alcohol (only with heating) and propylene glycol, and insoluble in benzene and *n*-hexane.

ROBAXIN Injectable has a pH between 3.5 and 6.0.

AFTER MIXING WITH I.V. INFUSION FLUIDS, DO NOT REFRIGERATE.

CLINICAL PHARMACOLOGY

The mechanism of action of methocarbamol in humans has not been established, but may be due to general CNS depression. It has no direct action on the contractile mechanism of striated muscle, the motor end plate or the nerve fiber.

NDA 11-790/S-046
Page 4

Pharmacokinetics

In healthy volunteers, the plasma clearance of methocarbamol ranges between 0.20 and 0.80 L/h/kg, the mean plasma elimination half-life ranges between 1 and 2 hours, and the plasma protein binding ranges between 46% and 50%.

Methocarbamol is metabolized via dealkylation and hydroxylation. Conjugation of methocarbamol also is likely. Essentially all methocarbamol metabolites are eliminated in the urine. Small amounts of unchanged methocarbamol also are excreted in the urine.

Special populations

Elderly

The mean (" SD) elimination half-life of methocarbamol in elderly healthy volunteers (mean (" SD) age, 69 (" 4) years) was slightly prolonged compared to a younger (mean (" SD) age, 53.3 (" 8.8) years), healthy population (1.5 (" 0.4) hours versus 1.1 (" 0.27) hour, respectively). The fraction of bound methocarbamol was slightly decreased in the elderly versus younger volunteers (41 to 43% versus 46 to 50%, respectively).

Renally impaired

The clearance of methocarbamol in 8 renally-impaired patients on maintenance hemodialysis was reduced about 40% compared to 17 normal subjects, although the mean (" SD) elimination half-life in these two groups was similar: 1.2 (" 0.6) versus 1.1 (" 0.3) hours, respectively.

Hepatically impaired

In 8 patients with cirrhosis secondary to alcohol abuse, the mean total clearance of methocarbamol was reduced approximately 70% compared to that obtained in 8 age- and weight-matched normal subjects. The mean (" SD) elimination half-life in the cirrhotic patients and the normal subjects was 3.38 (" 1.62) hours and 1.11 (" 0.27) hours respectively. The percent of methocarbamol bound to plasma proteins was decreased to approximately 40 to 45% compared to 46 to 50% in the normal subjects.

INDICATIONS AND USAGE

The injectable form of methocarbamol is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Methocarbamol does not directly relax tense skeletal muscles in man.

NDA 11-790/S-046
Page 5

CONTRAINDICATIONS

ROBAXIN Injectable should not be administered to patients with known or suspected renal pathology. This caution is necessary because of the presence of polyethylene glycol 300 in the vehicle.

A much larger amount of polyethylene glycol 300 than is present in recommended doses of ROBAXIN Injectable is known to have increased pre-existing acidosis and urea retention in patients with renal impairment. Although the amount present in this preparation is well within the limits of safety, caution dictates this contraindication.

ROBAXIN Injectable is contraindicated in patients hypersensitive to methocarbamol or to any of the injection components.

WARNINGS

Since methocarbamol may possess a general CNS depressant effect, patients receiving ROBAXIN Injectable should be cautioned about combined effects with alcohol and other CNS depressants.

Safe use of ROBAXIN Injectable has not been established with regard to possible adverse effects upon fetal development. There have been very rare reports of fetal and congenital abnormalities following in utero exposure to methocarbamol. Therefore, ROBAXIN Injectable should not be used in women who are or may become pregnant and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the possible hazards (see **PRECAUTIONS, Pregnancy**).

Use in Activities Requiring Mental Alertness

Methocarbamol may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle. Patients should be cautioned about operating machinery, including automobiles, until they are reasonably certain that methocarbamol therapy does not adversely affect their ability to engage in such activities.

Use in Patients with Hypersensitivity to Latex

The vial stopper contains dry natural rubber that may cause hypersensitivity reactions when handled by or when the product is injected in persons with known or possible latex sensitivity.

NDA 11-790/S-046

Page 6

PRECAUTIONS

General

As with other agents administered either intravenously or intramuscularly, careful supervision of dose and rate of injection should be observed. Rate of injection should not exceed 3 mL per minute-i.e., one 10 mL vial in approximately three minutes. Since ROBAXIN Injectable is hypertonic, vascular extravasation must be avoided. A recumbent position will reduce the likelihood of side reactions.

Blood aspirated into the syringe does not mix with the hypertonic solution. This phenomenon occurs with many other intravenous preparations. The blood may be injected with the methocarbamol, or the injection may be stopped when the plunger reaches the blood, whichever the physician prefers.

The total dosage should not exceed 30 mL (three vials) a day for more than three consecutive days except in the treatment of tetanus.

Caution should be observed in using the injectable form in patients with suspected or known seizure disorders.

Information for Patients

Patients should be cautioned that methocarbamol may cause drowsiness or dizziness, which may impair their ability to operate motor vehicles or machinery.

Because methocarbamol may possess a general CNS-depressant effect, patients should be cautioned about combined effects with alcohol and other CNS depressants.

Drug Interactions

See **WARNINGS** and **PRECAUTIONS** for interaction with CNS drugs and alcohol.

Methocarbamol may inhibit the effect of pyridostigmine bromide. Therefore, methocarbamol should be used with caution in patients with myasthenia gravis receiving anticholinesterase agents.

Drug/Laboratory Test Interactions

Methocarbamol may cause a color interference in certain screening tests for 5-hydroxy-indoleacetic acid (5-HIAA) using nitrosonaphthol reagent and in screening tests for urinary vanillylmandelic acid (VMA) using the Gitlow method.

NDA 11-790/S-046

Page 7

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies to evaluate the carcinogenic potential of methocarbamol have not been performed. No studies have been conducted to assess the effect of methocarbamol on mutagenesis or its potential to impair fertility.

Pregnancy

Teratogenic Effects-Pregnancy Category C

Animal reproduction studies have not been conducted with methocarbamol. It is also not known whether methocarbamol can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ROBAXIN Injectable should be given to a pregnant woman only if clearly needed.

Safe use of ROBAXIN Injectable has not been established with regard to possible adverse effects upon fetal development. There have been reports of fetal and congenital abnormalities following in utero exposure to methocarbamol. Therefore, ROBAXIN Injectable should not be used in women who are or may become pregnant and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the possible hazards (see **WARNINGS**).

Nursing Mothers

Methocarbamol and/or its metabolites are excreted in the milk of dogs; however, it is not known whether methocarbamol or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ROBAXIN Injectable is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of ROBAXIN Injectable in pediatric patients have not been established except in tetanus. See **Dosage and Administration, Special Directions for Use in Tetanus, For pediatric patients**.

ADVERSE REACTIONS

The following adverse reactions have been reported coincident with the administration of methocarbamol. Some events may have been due to an overly rapid rate of intravenous injection.

NDA 11-790/S-046

Page 8

Body as a whole: Anaphylactic reaction, angioneurotic edema, fever, headache

Cardiovascular system: Bradycardia, flushing, hypotension, syncope, thrombophlebitis

In most cases of syncope there was spontaneous recovery. In others, epinephrine, injectable steroids, and/or injectable antihistamines were employed to hasten recovery.

Digestive system, Dyspepsia, jaundice (including cholestatic jaundice), nausea and vomiting

Hemic and lymphatic system: Leukopenia

Immune system: Hypersensitivity reactions

Nervous system: Amnesia, confusion, diplopia, dizziness or light-headedness, drowsiness, insomnia, mild muscular incoordination, nystagmus, sedation, seizures (including grand mal), vertigo

The onset of convulsive seizures during intravenous administration of methocarbamol has been reported in patients with seizure disorders. The psychic trauma of the procedure may have been a contributing factor. Although several observers have reported success in terminating epileptiform seizures with ROBAXIN Injectable, its administration to patients with epilepsy is not recommended (see **PRECAUTIONS, General**).

Skin and special senses: Blurred vision, conjunctivitis, nasal congestion, metallic taste, pruritus, rash, urticaria

Other: Pain and sloughing at the site of injection

OVERDOSAGE

Limited information is available on the acute toxicity of methocarbamol. Overdose of methocarbamol is frequently in conjunction with alcohol or other CNS depressants and includes the following symptoms: nausea, drowsiness, blurred vision, hypotension, seizures, and coma.

In post-marketing experience deaths have been reported with an overdose of methocarbamol alone or in the presence of other CNS depressants, alcohol or psychotropic drugs.

Treatment

Management of overdose includes symptomatic and supportive treatment. Supportive measures include maintenance of an adequate airway, monitoring urinary output and vital signs, and administration of intravenous fluids if necessary. The usefulness of hemodialysis in managing overdose is unknown.

NDA 11-790/S-046

Page 9

DOSAGE AND ADMINISTRATION

For Intravenous and Intramuscular Use Only. Total adult dosage should not exceed 30 mL (3 vials) a day for more than 3 consecutive days except in the treatment of tetanus. ~~A like course may be repeated after a lapse of 48 hours if the condition persists.~~ If the condition persists, a like course may be repeated after a drug-free interval of 48 hours. Dosage and frequency of injection should be based on the severity of the condition being treated and therapeutic response noted.

For the relief of symptoms of moderate degree, one dose of 1 gram 10 mL (one 10 mL vial) may be adequate. Ordinarily this injection need not be repeated, as the administration of the oral form will usually sustain the relief initiated by the injection. For the severest cases or in postoperative conditions in which oral administration is not feasible, additional doses of 1 gram may be repeated every 8 hours up to a maximum of 3 g/day for no more than 3 consecutive days. ~~20 to 30 mL (two to three vials) may be required.~~

Directions for Intravenous Use

ROBAXIN Injectable may be administered undiluted directly into the vein at a **maximum rate of three mL per minute**. It may also be added to an intravenous drip of Sodium Chloride Injection (Sterile Isotonic Sodium Chloride Solution for Parenteral Use) or five percent Dextrose Injection (Sterile 5 percent Dextrose Solution); one vial given as a single dose should not be diluted to more than 250 mL for I.V. infusion. AFTER MIXING WITH I.V. INFUSION FLUIDS, DO NOT REFRIGERATE. Care should be exercised to avoid vascular extravasation of this hypertonic solution, which may result in thrombophlebitis. It is preferable that the patient be in a recumbent position during and for at least 10 to 15 minutes following the injection.

Directions for Intramuscular Use

When the intramuscular route is indicated, not more than five mL (one-half vial) should be injected into each gluteal region. The injections may be repeated at eight hour intervals, if necessary. When satisfactory relief of symptoms is achieved, it can usually be maintained with tablets.

Not Recommended for Subcutaneous Administration.

NDA 11-790/S-046

Page 10

Special Directions for Use in Tetanus

There is clinical evidence which suggests that methocarbamol may have a beneficial effect in the control of the neuromuscular manifestations of tetanus. It does not, however, replace the usual procedure of debridement, tetanus antitoxin, penicillin, tracheotomy, attention to fluid balance, and supportive care. ROBAXIN Injectable should be added to the regimen as soon as possible.

For adults: Inject one or two vials directly into the tubing of the previously inserted indwelling needle. An additional 10 mL or 20 mL may be added to the infusion bottle so that a total of up to 30 mL (three vials) is given as the initial dose (see **PRECAUTIONS**). This procedure should be repeated every six hours until conditions allow for the insertion of a nasogastric tube. Crushed ~~ROBAXIN~~ (~~methocarbamol~~) methocarbamol tablets suspended in water or saline may then be given through this tube. Total daily oral doses up to 24 grams may be required as judged by patient response.

For pediatric patients: A minimum initial dose of 15 mg/kg or 500 mg/m² is recommended. This dosage may be repeated every six hours ~~as indicated~~ if required. The total dose should not exceed 1.8 g/m² for 3 consecutive days. The maintenance dosage may be given by injection into tubing or by I.V. infusion with an appropriate quantity of fluid. See directions for I.V. use.

HOW SUPPLIED

ROBAXIN Injectable (100 mg/mL) supplied in 10 mL single dose vials in packages of ~~5 (NDC 0031-7409-87) and 25 (NDC 60977-150-01). 0031-7409-94).~~

Store at ~~controlled room temperature, between 20°C and - 25°C (68°F - 77°F), excursions permitted to 15° - 30°C (59°F - 86°F).~~

[insert necessary information here to reflect the change in NDA ownership from Wyeth-Ayerst to Baxter Healthcare Corporation]

Revised November 2003

Printed in U.S

This label may not be the latest approved by FDA.
For current labeling information, please visit <https://www.fda.gov/drugsatfda>